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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,641	08/30/2001	Philip A. Beachy	JHUC-P01-017	9388

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EXAMINER	
CHANDRA, GYAN	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,641	BEACHY ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,8-23 and 26-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 5, 8-23 and 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/12/2006 has been entered.

Status of Application, Amendments, and/or Claims

The amendment to claims 1 and 32 has been made of record.

Claims 1, 4, 5, 8-23 and 26-32 are pending and are under examination.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Response to Arguments

Rejections-maintained

Claim Rejections - 35 USC § 103

The rejection of claims 1, 4, 5, 8, 19 -27, and 29-32 under 35 U.S.C. 103(a) as being unpatentable over Sommers et al in view of Herrick-Davis et al, is maintained for reasons of record on p. 3-6 of Office Action mailed on 06/14/05.

Applicants agree that Sommers et al teach random and site directed mutageneis to substitute the aminoterminus and transmembrane regions of the STE2 gene in yeast for studying the aminoacid responsible for switching a receptor between active and inactive stages. However, applicants reiterate their arguments of 11/18/2005 (see Remarks on page 7 last paragraph continued through page 8) that Sommers et al do not teach providing a library of coding sequences for activating mutations of candidate receptor or ion channel wherein amino acids are replaced for small or medium side chain amino acids for large chain amino acids. They argue that Sommers would not have known which substitutions to make without first screening the library of random mutants. Further, Applicants argue that Herrick-Davis et al teach site directed mutagenesis to substitute amino acids with different polarity or longer side chains. Applicant state that individual references do not provide motivation to combine them together.

Applicants' arguments have been fully considered but have not been found to be persuasive because (as stated in the previous Office Action of 1/18/06) Sommers et al. teach a method for identifying constitutively activating mutations by making a library carrying random as well as site directed mutations in the amino terminus and transmembrane regions of the STE2 gene (page 6899, left column, 2nd paragraph) in yeast and then screening for these mutations for the receptor activation. Sommers et al. teach that introduction of mutations in an a-factor receptor (a yeast G protein coupled receptor) to constitutively activate the receptor 2, 5, 7 or 20 fold. Further, Herrick-Davis et al teach application of site directed mutagenesis to substitute amino acids with longer

side chains or of different polarity with aromatic substitutions. They teach substitution of amino acids to increase in the binding affinity of 5HT to the mutant receptor (page 1140, left column, 3rd paragraph). Therefore, the person of ordinary skill in the art would have been motivated do so with a reasonable level of success to more efficiently study the effect of various mutations in side chain amino acids, within the residues of helical domain or the interfaces between transmembrane helices as taught by Sommers for constitutive activation of the receptor in order to increase the probability of finding novel therapeutic agents for antagonist, inverse agonist as taught by Herrick-Davis et al.

The rejection of claims 9-18 under 35 U.S.C. 103(a) as being unpatentable over Sommers et al in view of Herrick-Davis et al. as applied to claims 1, 4, 5, 8, 19 -27, 29-32 above, and further in view of Barak et al, is maintained for the reasons of record on p. 6-7 of Office Action mailed on 06/14/2005.

Applicants reiterate their arguments of 11/18/2005 (See Remarks, page 9) that Barak et al teach using a heterologous reporter system for determining activity but Barak et al do not teach using a library of site directed mutations. Applicant argues that there is no suggestion to combine Barak et al with Sommers and Herrick-Davis and therefore, one skill of the art would not epect to be successful in combining the disclosure of Barak with Sommers and Herrick-Davis to arrive at the instantly claimed invention.

Applicants' arguments have been fully considered but they are not persuasive because Sommers et al teach identification of constitutively active mutations by making

a library carrying random as well as site directed mutations in the amino terminus and transmembrane regions of the STE2 gene in yeast and then screening for these mutations for the receptor activation. The person of ordinary skill in the art would have been motivated to study the effect of various constitutive mutations for finding novel therapeutic agents for antagonist, inverse agonist as taught by Herrick-Davis in a mammalian heterologous reporter system as Barak et al teach using GFP reporter system to measure the activation of a GPCR that can be used to study constitutive mutations.

The rejection of claim 28 under 35 U.S.C. 103(a) as being unpatentable over Sommers et al in view of Herrick-Davis et al and Barak et al, as applied to claims 1, 4, 5, 8-27 and 29-32 above and further in view of Lerner et al, is maintained for the reasons of record on p. 7-9 of Office Action mailed on 06/14/05.

Applicants reiterate their arguments of 11/18/2005 (See Remarks, page 10) that Lerner et al disclose identifying antagonists or agonists for G-protein coupled receptor using a pigment cell. However, they do not teach use of a library of site directed mutations generated by replacing coding sequences to study constitutive activation and that there is no motivation to combine set forth references.

Applicants' arguments have been fully considered but they are not persuasive because the person of ordinary skill in the art would have been motivated to study the effect of various constitutive mutations for finding novel therapeutic agents for antagonist, inverse agonist as taught by Herrick-Davis in a mammalian pigment

aggregation system as taught by Lerner et al by measuring activation of GPCR through changes in the level of cAMP in a frog melanophore assay.

The rejection of claims 1, 4, 5, 8, 10, 19-24, 26, and 29-32 under 35 U.S.C. 103(a) as being unpatentable over Herrick-Davis et al. in view of Dahiyat et al., is maintained.

Applicant agrees that Herrick-Davis discloses that the muation of amino acid 312 from serine to phenylalanine or lysine in the serotonin 5-HT receptor activates the receptor. Applicant also agrees that Herric-Davis expresses the library in a mammalian host cell. However, applicants reiterate their arguments of 11/18/2005 (see Remarks, page 10 through page 11) that Herrick –Davis does not teach providing a library of coding sequences for potentially activating mutations of the candidate receptor protein. Applicant argues taht Herrick-Davis does not teach measuring receptor activation with an indicator gene. Further, Applicant agrees that Dahiyat teaches a method of designing a protein library. However, Applicant argues that Dahiyat does not limit the mutations to replacing coding sequences for small or medium side chain amino acids with coding sequences for large side-chain amino acids, as being instantly claimed.

Applicants' arguments have been fully considered but they are not persuasive because Herrick-Davis teach that the constitutive G protein coupled receptors have been synthesized in vitro by mutating specific amino acids within different regions of the intracellular loop or transmembrane domains (page 1138, 1st paragraph). Further, they state " we attempted to alter the tertiary structure by substituting amino acids with

longer side chains or of different polarity with aromatic substitutions (page 1139, top of the left column), this does encompass the limitation of providing a library of coding sequences. They teach that the replacement of the native amino acids with amino acids having long basic or acidic side chains produce greater degree of constitive activity, whereas replacement with aromatic amino acids produce intermediate degree of constitutive activity (page 1140, 1st paragraph of heading Resutls). Herrick-Davis state that the consitutive active receptors provide unique model systems for studing the active conformation of the receptor, delineating specific regions of the receptor involved in G protein coupling, and for testing drugs for their ability to enhance or inhibit constitutive second message activation (page 1143, last paragraph).

Applicants' arguments regarding Dahiyat have been fully considered but they are not persuasive because Dahiyat teaches a method of designing a protein library for the substitution of residues in any part of a protein including the buried core, the solvent exposed surface, and the boundary between core and surface (page, 82, 2nd paragraph). They teach that a protein sequence can be designed to accomplish a library of a protein having various changes in the amino acids (hydrophobic) within the core structure, side chains or in the amino acids (hydrophilic) on the surface of a protein (page 82, middle column, 1st paragraph). The skill of art is high and one of skill in the art would know the nature of an amino acid; whether it is a hydrophobic, hydrophilic or it has a short side chain or a long side chain. Dahiyat et.al. teach modifying core position amino acids using A, V, L, I, F, Y or W, modifying the surface amino acids using A, S, T, H, D, N, E, Q, K, or R (page 83, left column, continuing paragraph from page 82),

whereas, the boundary position of a protein using a combination the amino acids as described above.

The rejection of claims 9, 11-18, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herrick-Davis et al in view of Dahiyat et al. as applied to claims 1, 4, 5, 8, 10, 19-24, 26, and 29-32 above and further in view of King et.al, is maintained for reasons of record as Office Action mailed on 12/15/2004.

The rejection of claim 28 under 35 U.S.C. 103(a) as being unpatentable over Herrick-Davis et al. in view of Dahiyat et al. as applied to claims 1, 4, 5, 8, 10, 19-24, 26, and 29-32 above and further in view of Lerner et al, is maintained for the reasons of record in the previous Office Action.

Applicants reiterate their arguments of 11/18/2005 (see Remarks, page 11-12) that King does not disclose providing a library of coding sequences for potentially acitivating mutations of a candidate receptor or ion chanel, wherein library is generated by replacing coding sequences for small or medium side chain amino acids with coding sequences for large side chain amino acids. Applicant argues that King does not disclose expression of a library of mutant alleles in mammalian host cells to determine constitutive activation. Further, Applicant argues that Lerner also does not use a library of site directed mutations, wherein the library is generated by replacing coding sequences for small or medium side chain amino acidss with coding sequences for large side chain amino acids.

The teachings of King and Lerner are summarized as set forth in previous Office Action of 12/15/2004. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

No claim is allowed.

This is a request for continued examination under 37 CFR 1.114. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1646
19 July 2006
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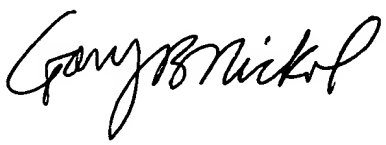

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